BIOGRAPHY.

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THOMAS ADDISON: PIONEER OF ENDOCRINOLOGY*

BY

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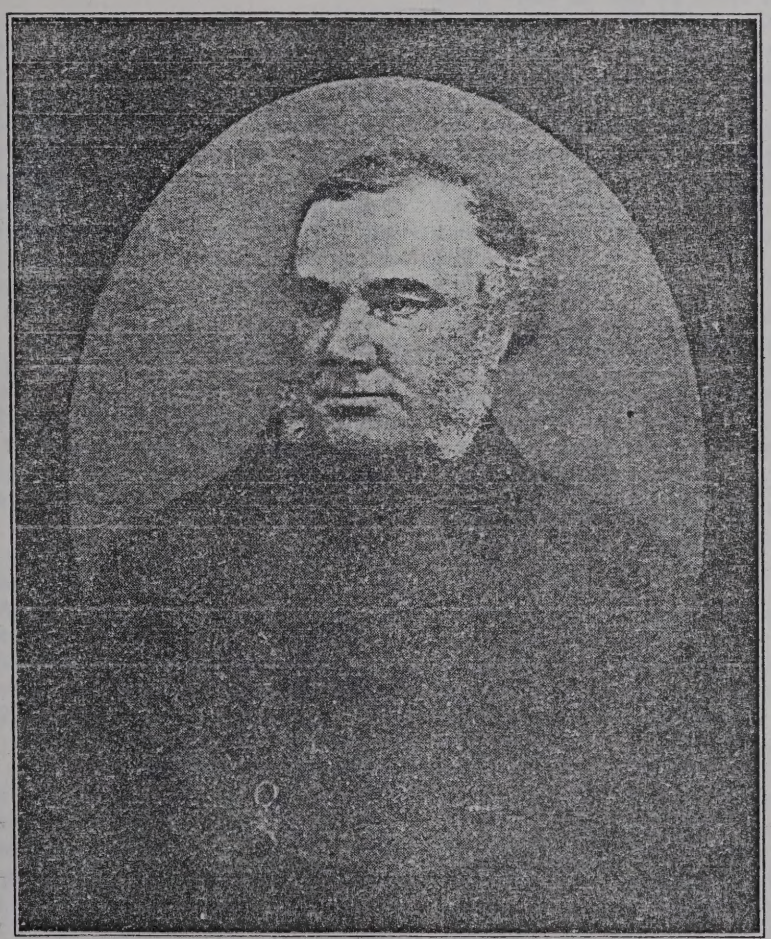
Thomas Addison was second in that matchless succession of physicians and morbid anatomists—Richard Bright, Thomas Addison, William Gull, and Samuel Wilks—whose work at Guy's Hospital in the earlier and middle years of the nineteenth century raised to such heights the reputation of this school as a great centre of medical teaching and investigation, and contributed so much to the foundation of the great nineteenth-century tradition of advancing medical knowledge by the accurate study and differentiation of diseases in the clinic, closely linked with an equally thorough scrutiny of their results as seen after death. The names of two of them, Bright and Addison, have been permanently associated with diseases which they thus described; the number would be three if we included the name of Thomas Hodgkin, who was curator of the museum here in the same period, though never on the clinical staff. Two of them again, Addison and Gull, can be regarded as clinical pioneers of endocrinology. In Gull's case we ought to associate his achievement with that of another and younger Guy's physician, Hilton Fagge, whose recognition of absence of the thyroid as the cause of cretinism enabled Gull, in 1874, in describing "a cretinoid condition in adult women" now known as myxoedema, to associate it with atrophy and functional defect of that gland. That, however, was a quarter of a century later than Addison's first mention of a condition which he had discovered, now known everywhere as Addison's disease, and which he then described as "a remarkable form of anaemia" regularly associated with disease of the suprarenal capsules.



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Two Pioneer Communications

The late Sir William Hale-White,† whose long life enabled him to transmit to more than one later generation the great tradition of this school from a time when Addison was still held in living memory here, has suggested that "the whole of endocrinology dates from March 15, 1849"—this being the date on which Addison made the first, short communication on his disease to the South London Medical Society. I believe that a good case could be made for that claim. There had, indeed, been earlier accounts of diseases—diabetes mellitus and exophthalmic goitre—which were shown much later to have a causal relationship to endocrine disorders. Even cortical tumours of the suprarenals had been recorded early in the nineteenth century, and hirsutism noted in a girl patient, but again without clear recognition of an aetiological relationship. I think, therefore, that we may agree with Sir William Hale-White that

*The Addison Lecture given at Guy's Hospital on June 23.

†*Great Doctors of the Nineteenth Century.* Sir W. Hale-White. Arnold and Co. 1935. To those who wish to learn more of Addison's life, personality, and achievements, the chapter on him in that volume is recommended. It gives references to other accounts of him by Samuel Wilks, who was his pupil, and Lonsdale, a lifelong medical friend.

endocrinology began effectively with Addison's paper, which in 1849 made the first clear attribution of a general morbid condition to defect of a ductless gland; and you will note that the date gives a centenary character to our celebration of this great man and his achievement.

Addison's fuller account of the disease which now bears his name was published six years later, in 1855, as a separate slender quarto with fewer than 46 pages of large printed text, richly illustrated with coloured lithographic plates and bearing the title *On the Constitutional and Local Effects of Diseases of the Suprarenal Capsules*. You will note that even the title emphasizes the aetiological inference. On these two pioneer communications by Addison the author of a recent textbook on the now enormous science of endocrinology makes apt comment: ". . . They show how much can be accomplished, without any of the modern clinical and laboratory facilities, by keen observation of the living and dead patient. They are prominent examples of concise and descriptive medical writing." They are so indeed; no better model could be recommended to the many who to-day seek to give permanent record to observations which are, in the main, of slighter significance.

A remarkable feature of the publication of 1855 is that, by way of introduction to the principal theme, Addison describes and differentiates another new disease, for which, by contrast, he had failed to discover an adequate cause by examination post mortem. This he named "idiopathic anaemia," but it is now generally known as "pernicious" or "Addison's" anaemia. It is not clear that he had at first distinguished with certainty between these two fatal diseases, in both of which anaemia and lassitude were prominent; but there is no doubt about the distinction in the book of 1855. His object there was to give an exact account, based on a series of cases, of what he called "bronzed skin" or "melasma suprarenale," known to us as "Addison's disease." The description of "idiopathic anaemia" is given only by way of introduction, to explain that the author was looking for additional cases of this condition when, in his own phrase, he "stumbled upon" another major discovery, which is the main subject of the book.

So that this slender volume contains the first full description of two new diseases; and, to quote Sir William Hale-White again, "Addison's account of each is so perfect that nothing has been found wrong in his clinical picture, and nothing has been added except facts that have been obtained by instruments which he did not possess, and a few occasional symptoms not present in the cases which he describes." I think it should be added that, if Addison had looked at the marrow in the long bones of the patients dying of pernicious anaemia, his acute eye could hardly have missed its unusual appearance. Even without any of the technical equipment which has made haematology a later possibility, he might in this case also have associated what he could see post mortem with the general disease. He certainly could not have foreseen, however, that the bone-marrow defect and the consequent anaemia would be traced many years later, in 1926, to the failure of a kind of endocrine control normally exercised by the liver; and even remoter from any conception possible to Addison, or to anybody till very recent years, is the news from two different research centres, in America and this country, of the isolation this year of the immensely active agent responsible for this endocrine control of the haematopoietic function, and the remarkable discovery that cobalt is an important element of its composition. Perhaps we may regard that, too, as an achievement suitably commemorating the fact that pernicious anaemia, which this potent hormone (or vitamin) so dramatically relieves, was first recognized by Addison about 100 years ago.

Other Achievements

When Addison's book describing these diseases was published in 1855 he was already 60 years of age. It would be very remarkable if he had first begun to make and to publish discoveries of such outstanding merit so late in life. In fact, he had already made and published others in an impressive series; and some of these, in particular those dealing with pneumonia and phthisis, were regarded by his pupil Wilks as the highest of all his achievements. What is really remarkable is that they should have been so little recognized and so widely forgotten. His earliest publication of importance was a characteristically perfect description of the clinical appearance which he found to be associated with, and diagnostic of, a fatty liver. Then in 1839, when he was 44 years old, in a book, *Elements of the Practice of Medicine*, which he published with his senior, Richard Bright, Addison gave the first descriptions of appendicitis and its consequences—"descriptions," according to a modern writer, "so clear and well presented that they could not be surpassed to-day." Later he gave the first correct account of the pathological process of lobar pneumonia; he published observations calling for a profound modification of the earlier conception, due to Laennec, of the destructive process in pulmonary phthisis; and he discovered and described xanthoma, which he called "vitiligoidea." And all these contributions to the advancement of medical knowledge, any one of which might be judged adequate by itself to have given him high rank as an investigator, were made by Addison before he discovered the two diseases which bear his name and thereby keep it in general remembrance among those who study and practise medicine.

When Addison came to London after graduation in Edinburgh, he gave his time and interest for some years chiefly to diseases of the skin. This interest he retained after he had begun his career at Guy's, where he entered as a student in 1817; it was he who later superintended the making of the beautiful wax models of skin conditions which are still one of the great treasures of the pathological museum here. He seems to have been rather a proud and shy man, not easy of approach; but none of the Guy's men in that great succession stood higher in reputation with his colleagues and pupils as a physician or as a teacher. Much of his time was spent, and practically the whole of his professional interest was centred, in this hospital. Outside it he sought no recognition, and he received but little. Only late in his career was he elected to the Fellowship of the Royal College of Physicians, and he held neither lectureship nor office there. He was never even proposed for the Fellowship of the Royal Society, and he was never a physician to the Court. Here you will keep him in proud memory as the greatest of all, perhaps, of the great medical investigators and teachers who were members of the staff of this hospital in that period. As his pupil, Samuel Wilks, wrote of him: "For many years he was the leading light of Guy's, so that every Guy's man during the thirty or forty years of his teaching was a disciple of Addison, holding his name in the greatest reverence, and regarding his authority as the best guide in the practice of his profession."

The Development of Endocrinology

In the medical circles of a wider world Addison will be remembered chiefly as a pioneer of the science of endocrinology—as the man who first entered and opened to other explorers a new territory which in the intervening century has been extended in all directions and brought under a most vigorous cultivation. There have been periods in which doubts of its further fertility have become prevalent and have seemed even to be natural, but it is to-day yielding harvests of medical knowledge in overwhelming abundance and in bewildering variety. I am going to invite you now to follow me in a preliminary survey, at the best a most cursory review, of the lines of development along which the present position has been reached. Then I shall endeavour to speak in somewhat greater detail of the course of the advance, including some recent and intricate phases, of knowledge of the endocrine functions of the particular ductless glands, the suprarenals, which, through Addison's discovery, provided endocrinology with the point of its very beginning, and which are now providing a focus for some of its most recent and most rapidly progressive developments.

I think we may assume that, brilliant and accurate observer as he was, Addison went as far as it would ever have been possible to proceed with the advancement of knowledge of an endocrine defect by simple observation of the results of a natural process at the bedside and in the post-mortem room. His work came at the end of the purely observational period and at the beginning of a new epoch, in which deliberate experiment was to play a dominant part. It is curious, indeed, that the use of the experimental method in medicine should have fallen so long into abeyance. William Harvey had shown what it could do, and had particularly enjoined its use on his fellow physicians, two centuries earlier; but before Addison's day English physicians appear to have forgotten Harvey's injunction, and to have left the use of experiment to surgeons like John Hunter and Charles Bell. And when a major revival of the experimental method came, opening the era in which we are still living, it began, not in Harvey's England, but on the European continent.

There, in Paris, the founder of modern physiology, Claude Bernard, in his experimental studies of the glycogenic function of the liver had reached and propounded the general idea of an internal secretion into the blood. The idea was not an entirely new one; its germ can be found in medical writings at least as early as 1775; but Bernard gave it form and an experimental basis. He was not directly concerned, however, with the specifically acting internal secretions of the glands with which endocrinology normally deals; and, apart from what had been known since prehistoric times of the effects of castration, the first attempt to study the function of an endocrine organ by deliberate experiment must apparently be credited to Brown-Séquard, who began to remove suprarenal glands from animals by operation in 1856, the year after Addison's book was published. His animals all died rapidly; but any significance which his results might otherwise have claimed seems to be called in question by his frequent record of fatality following unilateral adrenalectomy—an operation which later workers, using a clean surgical technique, have uniformly found harmless. In any case, neither he nor Tizzoni (1886), nor Abelous and Langlois (1891), who thus later confirmed the fatal effect of double adrenalectomy, contributed much more than a confirmation of Addison's conclusion, from his study of Nature's experiments, that the function of the suprarenals was for some reason a vital necessity.

It was in 1856, again, that Moritz Schiff reported that extirpation of the thyroid gland was fatal to dogs—many years, it will be realized, before the clinical studies of Fagge and Gull brought to light the connexion between defect of thyroid function and cretinism or myxoedema. There can be no doubt, however, that the effect which Schiff thus early observed was mainly due to his removal of the parathyroid glands with the thyroid, to which in the dog they are closely attached. This was eventually made clear by the work of Gley in 1891; but, before this, Schiff had himself shown that successful grafting of a portion of a dog's thyroid gland, which presumably contained a parathyroid, would protect it from the normally fatal result of removing the remainder. And after Gley's demonstration of the separate function of the parathyroid glands the possibility and protective effect of grafting these alone was shown by von Eiselsberg (1892), Leischner (1909), and others.

Meanwhile the experience of Reverdin and of Kocher on the myxoedematous or cachexial condition following surgical removal of the human thyroid for goitre, and Horsley's production in 1884 of an artificial myxoedema by thyroidectomy in the monkey, had brought the experimental work on the thyroid again into closer relation with the observed results of its atrophy in man. And then in 1891 came the first successful application of these experimental findings in practical therapeutics, when Murray, of Newcastle, showed that myxoedema could be successfully treated by administering an extract of sheep's thyroid—a notable milestone, indeed, on the road of advance in endocrinology. In this case, at least, the formation of an internal secretion was no longer a matter of inference; it had become a demonstrated fact.

This advance was followed, however, by a long and discouraging delay, which was especially obvious on the side of remedial application. When I myself, as a student, first began to be conscious of physiology and its progress, Horsley's experimental results and Murray's triumphant application of them were still relative novelties, and there was great interest in the likelihood of analogous therapeutic success in diseases due to defects of other ductless glands. As the years went by, however, such possibilities seemed to become increasingly remote. Plenty of observers were trying to correct such defects, whether resulting from disease or from experimental removal, by administering glands in substance or as artificial extracts; but no convincing success was for many years obtained in such other cases—neither with the parathyroid and suprarenal glands, nor with the gonads, nor with the pancreas, the removal of the latter having been found by Minkowski, in 1889, to cause a diabetes mellitus. With all these glands, on the other hand, protection against the effects of removal was obtainable by the establishment of successful grafts in advance.

It began to be believed, and the conviction grew and hardened with time, that the thyroid might be unique among these presumptively endocrine organs in the stability of its active principle, or in the extent to which this was stored in the gland so as to be available at a given moment for extraction. It had not, indeed, been established even yet, by strict evidence, that these other organs had in fact an endocrine function: one or another of them, if not all, might conceivably act by destroying an injurious by-product rather than by supplying a factor necessary for normal metabolism. And while this position of doubt remained, the progress of endocrinology, especially on the side of remedial replacement, was of necessity halted. Thus there grew, for a time, a discouraging tendency to suspect that the experimental method, like that of clinical observation

before it, might be approaching the limits of what it could achieve in this difficult field of inquiry. Then, after some thirty years, came the discovery of insulin by Banting and Best in 1921, revolutionizing the treatment of pancreatic diabetes, bringing a whole range of metabolic problems within the scope of new and progressive exploration, restoring to work on the ductless glands the earlier spirit of hopeful enterprise, and sounding the advance into a new phase, in which endocrinology is still expanding with a speed which now puts a strain on the alertness and the scientific equipment of anyone who endeavours to keep pace with its headlong progress and its dazzling changes.

There have, of course, been a number of other important factors of this astonishing acceleration. One has been the concentration of studies on the pituitary body, in the medical and surgical clinics as well as in the experimental laboratory, and especially on the control over the functions of other ductless glands which is exercised by the hormones of its anterior lobe—a control which led the late Sir Walter Langdon-Brown, and others who have adopted his picturesque phrase, to describe the pituitary anterior lobe as "the conductor of the whole endocrine orchestra." Another has been the rapid elucidation of the once baffling interplay of endocrine activities involved in the sexual cycle. Yet another and most important factor has been the discovery of the true plan of the chemical structure of the sterols and their derivatives, providing the key to the chemical nature and relationships of the whole series of steroid hormones, including, as we shall see, those of the suprarenal cortex as well as those of the gonads.

We must make no further attempt, however, to range over the whole endocrine landscape. Any one section of it, if an endeavour were made to deal with it in full detail, could now provide the material for a whole course of lectures by somebody equipped so to present it. For several reasons I must bring our inquiry now to a narrower focus, and in the rest of this memorial lecture I shall ask you to look with me, still in rather hasty survey, and without any pretence at more than an occasional reference or attribution, at some of the recent developments of knowledge concerning the subject of Addison's own pioneer investigation, the suprarenal glands.

The Suprarenal Medulla

We must recall first that it was not till 1895 that it began to be understood that the suprarenal body consisted of two functionally different glandular organs bound together as cortex and medulla. In that year Oliver and Schäfer discovered the remarkable immediate actions of simple extracts from the gland when these were injected intravenously or, as in later experiments by others, were applied locally. Then the active principle responsible for these intense immediate effects was found to be localized entirely in the medulla of the gland; and just after the end of the nineteenth century it was isolated, as adrenaline or epinephrine, and eventually made by synthesis.

Meanwhile it had been discovered by Lewandowsky and by Langley, and then further demonstrated in fullest detail by Elliott, to whom the pure adrenaline was available, that there was a remarkable and unquestionably significant correspondence between the actions of adrenaline and those of the true sympathetic nerves. It is well known how Elliott's penetrating early suggestion (1904) that sympathetic-nerve impulses transmit their effects by liberating small charges of adrenaline at the endings of the nerve fibres was verified many years later by Loewi's brilliantly simple and convincing experiments from 1921 onwards. It thus became a component of a now familiar and wider scheme which pictures the effects of all efferent peripheral nerve impulses as evoked by the liberation of one or another chemical transmitter at the nerve endings. There remained, however, some grounds for uncertainty whether the adrenergic transmitter was always, or entirely, "adrenaline" itself, though the correspondence was so close that nobody doubted that there was a definite chemical relationship. The late W. B. Cannon took care to leave the question open by referring to the transmitter always as "sympathin"; and, apart from a further hypothesis which led him to complicate this terminology, Cannon was clearly right in emphasizing the departures from complete identity between the actions, on the one hand, of artificially applied adrenaline and those, on the other hand, of sympathetic-nerve impulses and of the actual transmitter escaping from the site of its liberation into the blood stream and carried therewith to act on a distant organ. I myself, as early as 1910, had emphasized the tendency of adrenaline to exaggerate the inhibitor in relation to the augmentor components, as seen in the corresponding actions of sympathetic nerves. In comment on Elliott's hypothesis, I had even then pointed out that the primary amine corresponding to adrenaline (*nor*-adrenaline, then known commercially as "arterrenol") reproduced the actions of sympathetic impulses with an even closer fidelity, in this respect, than adrenaline itself.

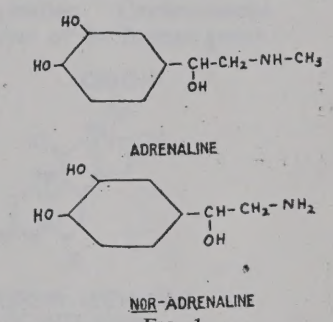

FIG. 1.

The evidence did not then seem to warrant a direct suggestion that *nor*-adrenaline might be the transmitting agent, or even a component thereof. Elliott's suggestion had at that time received but little notice, and *nor*-adrenaline was known then, and indeed till quite recently, only as a product of artificial synthesis.

But now, in the past year, the evidence has begun to flow in, arising simultaneously and independently in a number of different laboratories and in several different countries. Differential physiological reactions, contrived with much ingenuity and reinforced by fluorometric measurements, have made it possible to determine the proportional contributions of adrenaline and *nor*-adrenaline to the sympathomimetic activity of a fluid containing both. And by such methods it has been possible to prove that the sympathetic transmitter, as extracted from the sympathetic chain or from a purely adrenergic nerve, or found leaving the spleen in its venous blood during stimulation of its adrenergic nerve-supply, consists mainly of *nor*-adrenaline, with adrenaline itself as, at most, a minor component. Even the hormone secreted into the blood from the suprarenal medulla when the splanchnic nerve is stimulated, though it usually consists mostly of adrenaline during the early stages of such a stimulation, contains *nor*-adrenaline in increasing proportion as the process is repeated, and may even, after several periods, consist almost entirely of this primary amine.

These discoveries have interest for the pharmacologist and the chemist, and they remove certain puzzling discrepancies, but they make no fundamental difference to our conception of the endocrine function of the suprarenal medulla. We still regard it, following Cannon, as contributing immediate reinforcement to sympathetic-nerve actions on occasions of emergency, of sudden calls for

activity, or of emotional stress; and its hormone still figures also as the peripheral transmitter of the effects of adrenergic impulses. Only our conception of its chemistry is slightly changed. When first the actions of this medullary hormone were discovered it was natural to expect that a lack of it would be found to play at least an important part in the symptoms of Addison's disease, and evidence for such an effect of its exclusion was eagerly sought. As a result, however, we are left without any clear reason for attributing any conspicuous item of the Addisonian syndrome to simple lack of the endocrine function of the medulla. It is remarkably difficult, in fact, to detect any significant result from the removal of one suprarenal gland and extirpation of the medulla from the other. Even when Cannon removed, in addition, the whole system of the true sympathetic ganglia from cats, the animals remained healthy and exhibited only an unusual placidity. The fact that a melanin pigment is formed by oxidation of adrenaline or of its primary homologue might well suggest a connexion between a medullary defect and the bronzed skin of Addison's disease. Even in that case, however, there is no direct experimental evidence. Extirpation of the medulla does not cause any comparable pigmentation, though the possibility still remains open that a disorder, rather than a suppression, of the medullary metabolism normally producing the adrenalines may be responsible for the appearance of Addison's pigment.

What is now abundantly clear is that the main features of Addison's disease—the increasing debility and languor, the muscular weakness, the low arterial pressure, the decrease in blood volume, the disturbance of the normal balance of inorganic salts between body fluids and tissues, the liability to attacks of hypoglycaemia, and the general lack of the normal resistance to infection, poisoning, temperature changes, or any kind of harmful influence, this complex of symptoms leading to the inevitably fatal termination of untreated Addison's disease—are due entirely to the lack of the hormones formed by the cortex. It becomes ever clearer, indeed, that when Addison described his "melasma suprarenale" he was dealing with the collapse of a main arch of the functional structure by which a large proportion of the functions and reactions concerned in the maintenance of a healthy vitality are kept under endocrine control and regulation, and that the keystone of that arch was to be found in the hormones of the suprarenal cortex.

Cortical Hormones

After long discouragement and frustration, as an important item of the new and accelerating advance which set in after insulin was discovered, Swingle and Pfiffner in 1931 succeeded at length in preparing a stable and approximately purified extract of the cortical hormones by systematic injection of which life could be maintained in an animal deprived of its suprarenal glands. It was not long before, from several laboratories in different countries, crystalline fractions began to be obtained from cortical extracts, and a little later again the chemical nature of these began to be clarified. A few years earlier the chemical identification of pure hormones from the suprarenal cortex would have seemed an almost fantastic aspiration. Its achievement was greatly facilitated by the recognition, then recent, of the widely varied physiological significance of substances built by the attachment of different substituent groups and side-chains to a common hydrocarbon skeleton—the so-called cyclo-penteno-phenanthrene nucleus, forming the central structural feature of the sterols, the bile-acids, certain remedial glucosides, the steroid vitamin D, the steroid sex hormones, and, now, the steroid hormones of the suprarenal cortex. Many investigators have contributed to the amazingly rapid advance of knowledge of these substances, and mention can be made only of work by Kendall, and his co-workers of the research laboratories of the Mayo Clinic, in isolating several of these hormones from animal suprarenals, and of that of Reichstein, and his co-workers of Basle University, in producing members of the series artificially by synthesis.

At least six such active cortical steroids are known in pure crystalline form, and there is a highly active amorphous residue, probably containing a number of others. The evidence available concerning the different activities of those already isolated would by itself provide material for a course of lectures by an expert. In broadest terms, the hormones already recognized fall into certain main groups. The members of one such group are oxygenated at the carbon atom numbered 11 on the structural formula, while those of another group differ from the former only in having no oxygen in this position. Corticosterone (Fig. 2, I) is a representative member of the former group,

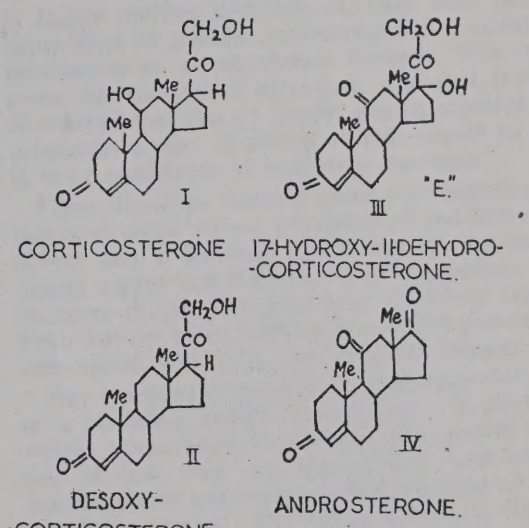

FIG. 2.

the actions of which are particularly concerned with carbohydrate metabolism. When given in excess they cause breakdown of cellular proteins, rise of blood sugar amounting to a temporary diabetes, with resistance to insulin, greatly increased excretion of uric acid, and a steep decline in the number of eosinophil leucocytes in the circulating blood. As a group, they may be regarded as the carbohydrate-controlling cortical hormones. A type of the other group is desoxycorticosterone (Fig. 2, II), and the characteristic action of these is to maintain the balance of inorganic salts in the body, with preponderance of sodium and chloride in the fluids and of potassium and phosphates in the cells. Lack of these hormones, which may be referred to as the salt-controlling group, causes loss through the urine of sodium and chlorides from the blood and body fluids and appearance in these of excess of potassium; administration of these hormones in excess causes over-retention of sodium and chlorides and water-logging of the tissues. Both these types of endocrine control are deficient in Addison's disease, and both must be replaced to preserve life, though lack of salt-controlling hormones can to some extent, and for a time, be made good by an added intake of sodium chloride. And there is another group, derivable from the 11-oxygenated series by replacement of the side-chain on the 17-carbon atom by oxygen; and the members of this group, of which

androsterone is a type (Fig. 2, IV), closely related to testosterone, the hormone of the testis, have indeed a sex-hormonal virilizing action.

Conclusion

The outlines are beginning to appear of the most complicated pattern of the complementary actions of these hormones in relation to one another; of their balanced actions against those of other hormones—for example, of some of them against the actions of insulin; and of the control of their formation and output by the so-called adrenocorticotropic hormone of the pituitary anterior lobe and apparently to some extent by the suprarenal medullary hormone adrenaline. I myself observed, as early as 1921, that a cat from which the suprarenals had been removed showed a greatly exaggerated sensitiveness to histamine, even before overt general signs of deprivation appeared. And, in more general terms, the part played by the cortical hormones in the whole scheme of the endocrine control of the body's functions and reactions, and especially, as Selye, of Montreal, has emphasized, in its adaptative reactions to almost all kinds of injury or stress, is undoubtedly one of central importance.

In further and most suggestive illustration of this function, in the case of at least one of the corticosteroids comes the recent news of therapeutic trials, at the Mayo Clinic and elsewhere, giving promise of a protective and curative effect of another member of the carbohydrate-controlling group, the 17-hydroxy-11-dehydrocorticosterone (Kendall's "Substance E," Fig. 2, III), against defective or perverted adaptative reactions responsible for rheumatoid arthritis. We shall wait eagerly for further evidence of advance in this new and surprising direction. And meanwhile I think you will agree that, if the anterior pituitary lobe occupies the conductor's rostrum in the endocrine orchestra, we must at least assign the leading violinist's desk to the suprarenal cortex. And surely no artificial monument to the memory of Thomas Addison could be so imposing as this great and now so rapidly growing tree of health-giving and life-saving knowledge, sprung from the seed which Addison dropped as he worked in this hospital with such patient devotion and with a clinical vision unsurpassed in its clarity and alertness.

The Report of the Food Investigation Board for the year 1939 has now been issued by His Majesty's Stationery Office, price 2s. 6d. Before publication could be effected when the report was originally prepared the type was destroyed by enemy action, and the document could not be issued until the present time because of restrictions on printing and paper. Some of the work described in the original paper has now been completed, and accounts have been published in various journals, to which references are given. Among the experiments described are tests on the control of microbial spoilage in meat by ultra-violet irradiation. Some retardation of bacterial growth was obtained, but the effect was not great. The storage of eggs was investigated, and experiments were carried out on freezing and storage of sprats before canning. Work was undertaken on the effect of acetylene and ethylene on the ripening of "Kelsey" South African plums. Treatment with either gas for three days accelerated ripening and improved the quality of the fruit, while untreated samples kept in air ripened slowly. Continued exposure to acetylene until the fruit ripened, however, made it too sweet. Research on blemishes on the rind of grapefruit stored at low temperatures, known as "low temperature spot," showed that wrapping in moisture-proof material instead of tissue-paper enabled lower temperature storage to be used, or the fruit to be stored longer. Other work included investigations of various methods of freezing strawberries, raspberries, and peas.

SOME PRINCIPLES UNDERLYING DETERMINATION OF SEX HORMONES*

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During the last two decades our knowledge of biological processes has been rapidly extending. Studies on sex hormones have had an outstanding influence on this advance. Research work and clinical experience have shown that specific principles formed in the pituitary, gonads, and adrenals profoundly affect the structure and function of the whole body. Therefore sex hormones, now available in highly purified preparations, have been introduced in many cases of gonadal and extragenital disorders either as substitution or as stimulation therapy. This use of hormones has enormously increased. However, it must always be remembered that no benefit can be expected from their promiscuous use. A critical attitude should be maintained in the management of endocrine disorders.

These disorders demand some understanding of sexual functions under various physiological and pathological conditions and a thorough knowledge of the hormone-producing organs and those involved in hormone metabolism. In cases of possible hormonal deficiency diagnosis and treatment are based both on the clinical picture and on the histological, biological, and chemical findings.

Any hormone determination is of value only in the light of a preceding clinical examination. Typical changes in weight, temperature, fatigue, appetite, growth and distribution of hair, and vascular, nervous, and other physical manifestations sometimes suggest the kind of sex-hormone imbalance present. The sexual sphere, as the most sensitive to hormonal influence, is the one most readily involved. Undisturbed sexual function may already exclude important hormonal disorders. Administration of sex-hormone preparations in such cases may be unwise and even harmful.

Further information on hormonal activity is obtained from histological and cytological examinations. In women, endometrial biopsy and vaginal smears reveal the uterine and vaginal response to ovarian stimulation. They are the simplest means of determining ovarian function. They show whether an ovarian deficiency exists and whether the disturbance involves suppression in the follicular or luteal phase, or both. They are used not only as diagnostic aids but also as a control to the efficacy of treatment. These clinical findings, however, vary with the responsiveness of the organ involved and are predominantly qualitative in character. They have to be completed by quantitative studies of sex hormones, data of which are provided by biological and chemical methods indicating hormone levels in blood and urine. These give evidence not only of the kind but of the amount of hormone produced. These determinations represent one of the most important diagnostic

*From a lecture delivered by Professor de Watteville to the Faculty of Ophthalmologists of London, at the Maternité of Geneva, on May 11, 1948.